Prions and antiprions

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DOI: https://doi.org/10.1515/bchm.1997.378.12.1393

Biol. Chem., Vol. 378, pp. 1393 – 1395, December 1997

Guest Editorial

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In the present issue of *Biological Chemistry*, Kristina Rother and colleagues describe their phylogenetic study of a long open reading frame (ORF) antiparallel to *Prnp*, the sequence encoding the cellular prion PrPc (see also Goldgaber, 1991; Moser *et al.*, 1993). Surprisingly, this 'antiprion' ORF is very nicely conserved across a well-assorted zoo – only marsupials and birds seem to have opted for getting by without it. This rather mysterious phenomenon is not unique to *Prnp*, and indeed the authors have extended their study to a heat shock protein, Hsp70, which shows an analogous behavior (Rother *et al.*, 1997).

The timing of Rother's publication seems appropriate: it once again reinforces the notion that, whenever prions are involved, more open questions than answers are available. This notion continues to apply – despite the recent award of the Nobel Prize for Physiology and Medicine to Stanley B. Prusiner – to both normal function of the prion protein and pathogenesis of prion diseases.

How did the prion saga develop? First formulated by J.S. Griffith in 1967 (Griffith, 1967), the 'protein-only' hypothesis states that the infectious agent causing transmissible spongiform encephalopathies (Kuru, Creutzfeldt-Jakob disease, fatal familial insomnia, BSE, sheep scrapie, and other related ailments) consists of the modified form of a normal cellular protein. Many years later, Stanley B. Prusiner achieved the biochemical purification of the hypothetical abnormal protein, which he called 'prion protein' (Prusiner, 1982). Leroy Hood, in collaboration with Prusiner, was then able to determine parts of the sequence of the prion protein (Prusiner *et al.*, 1984). Weissmann and coworkers cloned the cognate gene which, to the surprise of everybody who still had been betting on a conventional virus, indeed turned out to be encoded by the host genome (Basler *et al.*, 1986; Oesch *et al.*, 1985).

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These substantial discoveries allowed the protein-only hypothesis to be laid on firm scientific ground. A further landmark was the demonstration of linkage between familial forms of prion diseases and mutations in the prion gene (Hsiao *et al.*, 1989). Transgenic studies then identified the primary sequence of PrP as one main determinant of the species barrier of prions (Prusiner *et al.*, 1990). Finally, Weissmann and his colleagues created PrP knockout mice (Büeler *et al.*, 1992) and showed that they are resistant to infection with prions (Büeler *et al.*, 1993). Weissmann also achieved several important conceptualizations in the prion field, such as the 'unified theory' of prion propagation (Weissmann, 1991a), and the moiety termed PrP*, which is infectious but may differ from PrP^{Sc} (Weissmann, 1991b).

Although a conventional infectious agent has been invoked time and over to explain some atypical results (Lasmezas *et al.*, 1997; Manuelidis *et al.*, 1997), none of the latter results is, in our view, incompatible with the protein-only hypothesis. Taken together, the evidence in favor of one or another incarnation of the protein-only hypothesis is daunting. Whether Prusiner's concept of scrapie-associated PrP (PrP^{Sc}) being able to 'convert' PrP^{c} into a likeness of itself is correct, or whether aggregation and other mechanisms are involved (Eigen, 1996; Jarrett and Lansbury, 1993), remains to be seen.

So far, the normal function of the prion protein is also proving resilient to all attempts of clarification. It is hard to accept that PrP^{c}, a protein highly conserved through evolution whose gene is unrelated to any other known sequence, exists only to foster susceptibility to prion diseases. On the other hand, PrP^{c}-deficient mice suffer from preciously little defects: a synaptic phenomenon called *long term potentiation* which is presumed to be important for short-term memory and learning was reported to be impaired (Colling *et al.*, 1996; Collinge *et al.*, 1994) and can

be restored by transgenic complementation (Whittington *et al.*, 1995). While these experiments are quite compelling, an independent group using the mice generated in Zürich (Büeler *et al.*, 1992) failed to reproduce this finding (Lledo *et al.*, 1996). PrP^c-deficient mice generated with a different targeting construct lacking part of PrP intron 2 exhibit degeneration of cerebellar neurons in age (Sakaguchi *et al.*, 1996), but the claim that this is causally related to lack of PrP^c does hardly withstand critical scrutiny.

The function of PrP may be, of all things, related to its convertibility into PrP^{Sc}. Since immunization of mice with recombinant PrP^c has resulted in the production of a monoclonal antibody which exclusively recognizes PrP^{Sc} (Korth *et al.*, 1997), some structural equivalents of PrP^{Sc} may exist in liquid phase in an equilibrium with PrP^c, in a non-infectious and non-neurotoxic form. But why should that be so? Perhaps epigenetic propagation of structural information is advantageous for higher eukaryotes, since it is much faster than transmission of genetic traits, and can spread horizontally within the individuals belonging to one single generation. The yeast factor [PSI+] exists in two different states which spread non-genetically in a fashion which closely resembles PrP^{Sc}, yet confers to infected yeast cells advantageous properties (Chernoff *et al.*, 1995; Lindquist, 1996; Wickner, 1995; Wickner and Masison, 1996). This makes one wonder whether the prion principle may be much more widespread than is presently recognized.

So, what does the antiprion give? Conservatively, one might feel tempted to dismiss its significance on the basis of statistical considerations (which may explain the extraordinary length of its ORF), and because *Prnp* null mutant mice, in which both the PrP and the anti-PrP ORFs are disrupted, suffer from no obvious defects. While both arguments have a case, it is surprising that every mammalian (eutherian) species analyzed so far has such an uninterrupted reading frame, and the lack of an obvious phenotype in a knockout mouse does not exclude an important function for its cognate protein – the latter consideration applies, incidentally, also to the normal prion protein (Aguzzi and Weissmann, 1997; Prusiner, 1997). Clearly, functional studies are needed to address these fascinating questions.

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